PATENT APPLICATION
Attorney's Docket No. 262-011815

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Ludwig STÖCKL	:	**PROCESS AND DEVICE FOR THE PARALLEL PREPARATION OF AT LEAST 4n OLIGONUCLEOTIDES**
Serial No. Not Yet Assigned	:	
Filed Concurrently Herewith	:	

Pittsburgh, Pennsylvania
October 26, 2001

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington DC 20231

Sir:

Prior to initial examination, please amend the above-identified patent application as follows:

IN THE SPECIFICATION:

On page 1, after the title, please insert the following section headings and paragraph:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of International Patent Application Number PCT/EP00/03916 filed on May 2, 2000, entitled "Method And Device For the Parallel Manufacture Of Oligonucleotides" and designating, *inter alia*, the United States, which claims priority to German Patent Application Serial No. 199 19 607.9, filed April 29, 1999.

BACKGROUND OF THE INVENTION

Field of the Invention

On page 1, after the first complete paragraph, please insert the following section heading:

Description of the Related Art

On page 4, before the first complete paragraph, please insert the following section heading:

SUMMARY OF THE INVENTION

On page 12, please delete the second complete paragraph and insert the following replacement paragraph and section heading:

The process according to the invention is explained in more detail with the aid of an embodiment example of the device according to the invention with reference to the attached figures in diagram form.

BRIEF DESCRIPTION OF THE DRAWINGS

On page 12, please delete the sixth and seventh complete paragraphs and insert the following replacement paragraphs and section heading:

Fig. 4 shows a particular closing device for the reaction vessel outlet or reaction vessel inlet of a reaction vessel;

Fig. 5 shows a particular embodiment of a liquid feed device of the device according to the invention; and

Fig. 6 shows a particular embodiment of a liquid feed device of the device according to the invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

IN THE CLAIMS:

Please cancel claims 1-24 and add new claims 25-53 as follows:

25. A process for the parallel synthesis of at least 4n oligonucleotides, with the steps:

arrangement of at least four inserts each with n reaction vessels on a plate such that a first insert is at a first station, a second insert is at a second station, a third insert is at a third station and a fourth insert is at a fourth station, each reaction vessel containing an initiator base bound to an inert carrier, or a universal carrier,

carrying out in parallel of

a) a deblocking operation to remove protective groups simultaneously in all n reaction vessels of the insert at the first station,

b) a first washing operation simultaneously in all n reaction vessels of the insert at the second station,

c) a coupling operation for attaching individual nucleotides in all n reaction vessels of the insert at the third station, and

d) a second washing operation followed by a capping operation for blocking oligonucleotides which have not undergone the desired chain lengthening in the preceding coupling operation followed by a third washing operation followed by an oxidation operation for stabilizing the phosphate foundation matrix of the oligonucleotides, followed by a fourth washing operation simultaneously in all n reaction vessels of the insert at the fourth station, and

station by station rotation of the inserts through the four stations mentioned or of the stations relative to the inserts and carrying out of the above-mentioned operations until the

desired oligonucleotides have been formed by coupling of the individual nucleotides to one another.

26. The process according to claim 25, wherein at the second station, together with the first washing operation carried out there, a monitoring operation which provides information on the quality of the deblocking operation carried out at the first station takes place.

27. The process according to claim 26, wherein the monitoring operation comprises an on-line measurement of the conductivity of a washing liquid used for the first washing operation.

28. The process according to claim 26, wherein the monitoring operation comprises an on-line measurement of the colour intensity of a washing liquid used for the first washing operation.

29. The process according to claim 26, wherein the first washing operation is carried out until the monitoring operation shows that the protective groups removed in the preceding deblocking operation have been rinsed out completely.

30. The process according to claim 25, wherein in the coupling operation carried out at the third station, a selected nucleotide base is added to the reaction vessels simultaneously with an activator.

31. The process according to claim 25, wherein in the coupling operation carried out at the third station, a marking group is added to the reaction vessels.

32. The process according to claim 25, wherein the reaction vessels are constructed as flow-through vessels, each reaction vessel having an inlet and an outlet, and wherein the liquids to be fed to the reaction vessels in the four stations are conveyed into the reaction vessels and out of them by applying a pressure gradient between the reaction vessel inlet and reaction vessel outlet.

33. The process according to claim 25, wherein all the operations are carried out under an inert gas atmosphere.

34. A device for the parallel synthesis of at least 4n oligonucleotides, comprising

a first station for carrying out a deblocking operation,

a second station for carrying out a first washing operation,

a third station for carrying out a coupling operation,

a fourth station for carrying out a second washing operation followed by a capping operation followed by a third washing operation followed by an oxidation operation followed by a fourth washing operation, the first, the second, the third and the fourth station following one another at a distance in the circumferential direction,

a plate, which has at least four inserts each with n reaction vessels such that a first insert is at the first station, a second insert is at the second station, a third insert is at the third station and a fourth insert is at the fourth station, each reaction vessel being constructed as a flow-through vessel with a reaction vessel inlet and a reaction vessel outlet,

a device for carrying out a relative movement station by station between the plate and the stations,

a liquid feed device assigned directly to the reaction vessel inlets in each station, and

a drain channel assigned directly to each reaction vessel outlet in each station, each reaction vessel inlet being in tight engagement with the associated liquid feed device and each reaction vessel outlet being in tight engagement with the associated drain channel when the inserts are in a station, and there being a small axial distance at least between the reaction vessel inlets and the liquid feed device while a relative movement station by station between the plate and the stations takes place.

35. The device according to claim 34, wherein there is also a small axial distance between the reaction vessel outlets and the drain channels while a relative movement station by station between the plate and the stations takes place.

36. The device according to claim 34, wherein the plate is a rotary plate and wherein all the liquid feed devices are accommodated in or on a valve-carrying panel and all the drain channels are accommodated in a suction panel.

37. The device according to claim 36, wherein the valve-carrying panel has a flat contact surface to the upper side of the rotary plate and the suction panel has a flat contact surface to the underside of the rotary plate, and wherein the reaction vessel inlets are constructed flush with the upper side of the rotary plate and the reaction vessel outlets are constructed flush with the underside of the rotary plate.

38. The device according to claim 34, wherein each liquid feed device has n feed valves.

39. The device according to claim 36, wherein the valve-carrying panel and the suction panel are fixed against rotation, and wherein the rotary plate and the suction panel can be lowered relative to the valve-carrying panel.

40. The device according to claim 34, wherein each insert extends radially in the plate and has at least one row of reaction vessels.

41. The device according to claim 34, wherein the inserts are made of plastic.

42. The device according to claim 34, wherein each insert has on its longitudinal sides a coding groove of different construction or a coding projection which cooperates with a corresponding coding projection or a corresponding coding groove of the rotary plate.

43. The device according to claim 42, wherein the inserts can be assembled to reaction vessel panels by means of the coding grooves and the coding projections.

44. The device according to claim 34, wherein the reaction vessel outlet and/or the reaction vessel inlet of each reaction vessel has a constriction point which can be closed by a movable ball.

45. The device according to claim 44, wherein the ball is pushed in the direction of the constriction point by a force selected from the group consisting of gravity, the force of a spring, and magnetic force.

46. The device according to claim 34, wherein at least the liquid feed device of the third station has

a plurality of individual feeds, each of which is in liquid connection with the only one of the various liquids to be added to the reaction vessels at the station and the number of which corresponds to at least the number of different liquids to be added to the reaction vessels at the station,

a coupling drive for the individual feeds in order to connect each individual feed with a reaction vessel inlet as required, and

a common carrier for the individual feeds which can be displaced at right angles to the reaction vessel inlets.

47. The device according to claim 46, wherein the carrier is constructed as a carriage which can be displaced position by position, each reaction vessel inlet representing a position.

48. The device according to claim 46, wherein the coupling drive in a position of the carrier in which individual feeds are in alignment with reaction vessel inlets connected to a reaction vessel inlet only that individual feed which is connected to the liquid precisely required in the reaction vessel in question, and wherein, depending on the requirement, the carrier is then displaced optionally several times into another position in which individual feeds are in alignment with reaction vessel inlets and in which in turn the coupling drive connects to a reaction vessel inlet only that individual feed which is connected to precisely the liquid required in the reaction vessel in question.

49. The process according to claim 28, wherein measurement of the colour intensity is carried out by means of UV light.

50. The process according to claim 31, wherein the marking group is selected from the group consisting of a base analogue, a dyestuff and a hapten.

51. The process according to claim 33, wherein the inert gas atmosphere is selected from the group consisting of nitrogen, argon, and a nitrogen/argon combination.

52. The device according to claim 40, wherein each insert has two rows of reaction vessels parallel to one another.

53. The device of claim 41, wherein the inserts are made of polyether ether ketone.

REMARKS

Amendments have been made to the specification in order to conform the specification to standard United States Patent practice.

Original claims 1-24 have been canceled and new claims 25-53 have been added.

Examination and allowance of claims 25-53 are respectfully requested.

Respectfully submitted,

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MARKED-UP AMENDED SPECIFICATION PARAGRAPHS

Page 12, second complete paragraph

The process according to the invention is explained in more detail with the aid of an embodiment example of the device according to the invention with reference to the attached figures in diagram form. [In the figures:]

BRIEF DESCRIPTION OF THE DRAWINGS

Page 12, sixth and seventh complete paragraph

Fig. 4 shows a particular closing device for the reaction vessel outlet or reaction vessel inlet of a reaction vessel[, and];

Fig. 5 shows a particular embodiment of a liquid feed device of the device according to the invention; and

Fig. [5 and] 6 [show] shows a particular embodiment of a liquid feed device of the device according to the invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS